## REMARKS

Applicants thank the Examiner for acknowledging their claim amendments and their support for the amended claims and for reconsidering and withdrawing the § 112 (written description) and § 102 (anticipation) rejections.

**Rejection under 35 U.S.C. § 103**

Claims 44 and 53 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Ohuchida et al., U.S. Patent No. 7,176,240 ("Ohuchida") in view of Sramek et al., Opin. Invest. Drugs. 2002: 741-752 ("Sramek"). In particular, the Examiner argues that Ohuchida refers to treating and/or preventing neurodegenerative diseases, including Alzheimer's Disease ("AD"), using pentanoic acid derivatives, e.g., valproic acid. The Examiner concedes that, while Ohuchida provides a general recitation of various neurodegenerative diseases, it does not refer to Mild Cognitive Impairment ("MCI"). The Examiner then contends that Sramek cures this deficiency in Ohuchida because Sramek allegedly shows that drugs used to treat AD are also likely useful to treat MCI. The Examiner, thus, concludes that applicants' claims for treating MCI with valproic acid are obvious. Applicants traverse.

One of skill in the art at the earliest effective filing date of this application (October 22, 2002) would not have combined Ohuchida with Sramek. In fact, the Examiner's reliance on this combination was done solely with the benefit of hindsight based on applicants teaching for the first time that a pentanoic acid derivative (e.g., valproic acid) is effective in treating MCI.

The impermissible hindsight that has infected the Examiner's § 103 Ohuchida-Sramek rejection is evidenced by the cited documents themselves, as well as other more recent scientific literature. For example, Sramek reports only that treatment strategies tried in treating AD have been explored for treating patients with MCI: "all treatment strategies explored for MCI to date have been directly taken from those tried in AD" (p. 742; emphasis added). Sramek does not say, as the Examiner suggests, that AD drugs are used in the treatment of MCI. Certainly, Sramek never says or even suggests that AD drugs are useful in treating MCI.

Indeed, Sramek merely lists five general categories of potential therapeutic agents that had been tried in AD for exploration for treating MCI: acetylcholinesterase inhibitors, muscarinic agonists, free radical scavengers and antioxidants, sex steroid hormones, and anti-inflammatory agents. This no more than a research plan to see if a compound in any of those general categories can be used to treat MCI. It is not a specific teaching of a treatment for MCI using any specific compound. Further, Sramek, as a whole, makes plain that the many diverse potential therapeutic agents in these five general categories do not have a reasonable expectation of success for treating MCI. Indeed, as we demonstrate below, Sramek does not recite that any of his categories of agents, or specific agents within those categories, were actually successful in MCI clinical trials, or that any of the particular classes of compounds or specific compounds are actually used to treat MCI.

Sramek also acknowledges and tells the skilled worker the significant unknowns in MCI treatment: 1) that it is only plausible that at least some AD therapeutics will work in MCI and 2) that effectiveness remains to be determined. In fact, Sramek recites:

> "Whether or not these compounds will prove effective remains to be determined, however given the neuropathological correlates between the two conditions [AD

> and MCI], it is plausible that at least some AD therapeutics will be just as efficacious, if not more, in the treatment of MCI" (p. 745, second column; emphasis added).

These statements belie the Examiner's attempt to find in Sramek a teaching that drugs employed to treat AD are useful, or are reasonably expected to be useful, in treating MCI.

Sramek also confirms these earlier-acknowledged unknowns by reporting on clinical results of various treatments using compounds within these diverse categories of agents. Significantly, Sramek never reports that a compound or group of compounds is useful in treating MCI.

> (1) Acetylcholinesterase Inhibitors "AChEI"
>
> "[O]nly 15-40% of AD patients benefit from AChEIs and the improvements are primarily symptomatic without altering the neuropathology of the disease. Whether or not AChEIs would benefit MCI patients, or at least limit their conversion to AD is being investigated." (p. 746, first column)
>
> (2) Muscarinic Agonists
>
> "[A] clear demonstration of the benefit of muscarinic agonists for AD will likely need to occur before there would be sufficient interest in investigating these compounds in MCI." (p. 746, second column)
>
> (3) Free Radical Scavengers and antioxidants
>
> "Deciphering which factor or factors are responsible for the oxidative stress should yield not only a greater understanding of AD pathogenesis but also more effective therapeutic strategies for MCI." (p. 746, second column)
>
> "[A]dditional research remains to be done before the actual therapeutic value of the compound [Ginkgo biloba] can be determined." (p. 747, first column)
>
> "[D]espite these promising results, greater research is required before a conclusive judgment can be made in regards to vitamin C efficacy in MCI or AD treatment." (p. 747, first column – second column)

> "Despite these promising results, the paucity of clinical data makes it difficult to determine how effective anti-oxidant therapy can be for MCI or AD therapy." (p. 747, second column)
>
> (4) Oestrogen
>
> "[T]he majority of clinical trials conducted thus far have reported no clinically significant benefits associated with oestrogen therapy ... Indeed, a recent placebo-controlled study... showed no significant differences for the treatment groups on measures of cognition or mood." (p. 747, second column)
>
> (5) Anti-inflammatory agents
>
> "[I]t remains to be seen, which, if any anti-inflammatory compounds can effectively treat either AD or MCI." (p. 748, second column)

Therefore, Sramek itself confirms that the listed possible categories of agents, and specific agents within these categories, were not known to be useful to treat MCI, and that there was no reasonable expectation that they would be useful in that treatment.

More recent reports of the results of attempts to treat MCI, based on treatments tried for AD, likewise confirm that they are largely unsuccessful. See, e.g., Thal et al., A Randomized, Double-blind, Study of Rofecoxib in Patients with Mild Cognitive Impairment, Neuropsychopharmacology. 30[6], 2005: 1204-1215 ("Thal"); Petersen et al., Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment, 352(23), 2005: 2379-2388 ("Petersen"); Allain et al., Treatment of the Mild Cognitive Impairment (MCI), Human Psychopharmacology: Clinical and Experimental, 22(4), 2007: 189 – 197 ("Allain"). These documents are attached as Exhibits A, B and C, respectively.

Thal reports that the selective COX-2 inhibitor rofecoxib, an anti-inflammatory agent (Sramek's category 5), is ineffective in treating MCI:

> "We conducted a double-blind study [with rofecoxib]... in patients with mild cognitive impairment (MCI)... Analyses of... measures of cognition (e.g. the cognitive subscale of the AD Assessment Scale (ADAS-Cog)) and global function (e.g. the Clinical Dementia Rating (CDR)), did not demonstrate differences between treatment groups. There was also no consistent evidence that rofecoxib differed from placebo in post hoc analyses." (Abstract)

Petersen reports that the antioxidant vitamin E (Sramek's category 3) was not effective in treating MCI:

> "There were few significant differences in cognitive function from baseline between the vitamin E and placebo groups. The exceptions were in the scores for the executive, language, and overall cognitive score, and these were confined to the first 18 months of the study [and were not seen at the 24, 30, and 36 month time points]." (p. 2382, second column; see also Table 2)

Petersen further reports that although there were some differences in cognitive function in the case of treatment with donepezil, an AChEI (Sramek's category 1), its effects were limited. At 18 months, patients receiving donepezil were performing significantly better than placebo controls in 6 out 10 cognitive tests. At 24 months, the donepezil group was performing better in only one test, and no differences were seen at 30 and 36 months (see Table 2). Consequently, Petersen concludes: "our finding do not provide support for a clear recommendation for the use of donepezil in persons with mild cognitive impairment" (p. 2385, second column).

Allain reports that AChEI, antioxidants, sex steroid hormones, and anti-inflammatory agents (Sramek's categories 1, 3, 4 and 5) do not have therapeutic value in improving the memory performance deficits in MCI patients:

> "RCTs (Randomized clinical trials) assessing the therapeutic value of acetylcholinesterase-inhibitors (AChEIs) are negative either trying to improve symptoms (memory performance) or preventing the conversion from MCI to real Alzheimer's Disease (AD). The same negative results were obtained with... : non-steroidal anti-inflammatory compounds (rofecoxib), sex steroid hormones (testosterone, estrogens), or antioxidants (tocopherol)." (Abstract)

Thus, both Sramek and subsequent clinical evidence demonstrate that there is no correlation between treatments tried for AD and effective treatments for MCI. Therefore, a combination of Sramek and Ohuchida in the context of the claimed valproate treatment of MCI could have only been made with the benefit of hindsight and, in particular, knowledge of applicants' invention. For this reason alone, the claims are patentable over the cited documents.

Further, even if Sramek with Ohuchida were combined (which applicants argue would not have been done), the combination would not have suggested to the skilled worker that valproic acid would be useful in the treatment of MCI. As discussed above, Sramek confirms that the listed possible categories of AD treatment agents, and specific agents within these categories, were not known to be useful to treat MCI, and that there was no reasonable expectation that they would be useful in that treatment. In fact, Sramek reports that 4 out the 5 categories he points to lack results that would potentially support their use in treating AD, let alone MCI, and even those compounds that at least appear to benefit AD patients (albeit only symptomatically, i.e., AChEIs), are not known to be beneficial to patients with MCI. That question, says Sramek, is still under investigation. For these reasons, even if Sramek and Ohuchida were combined (which applicants argue would not have been done), it would not have suggested to the skilled worker that valproic acid would be useful in the treatment of MCI. And, even if the skillful worker decided to try valproic acid, rather than a compound falling within any of the categories of agents referred to in Sramek (an unlikely and unreasonable choice in itself because Sramek never even mentions a category of compounds that would include valproic acid), that worker would have no reasonable expectation that valproic acid would successfully treat MCI.

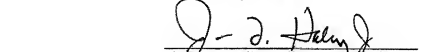
Finally, Ohuchida teaches away from the claimed invention. Ohuchida recites that certain pentanoic acid derivatives are expected to be useful for prevention and/or treatment of neurodegenerative diseases. Specifically, Ohuchida refers to treatment of neurodegenerative disease that is attributed to abnormal/reactive astrocytes (see, column 3, lines 7-34 and column 31, lines 15-29 of Ohuchida). However, as was explained at length in applicants' response to the February 8, 2008 Office Action, MCI is not a neurodegenerative disease. Because any supposed motivation for using pentanoic acid derivatives to treat AD, as reported in Ohuchida, is specifically connected to the ability of such compounds to reduce neurodegeneration, a skilled worker would not expect pentanoic acid derivatives to be useful in MCI, a condition where neurodegeneration is not present. Therefore, even with Sramek, it would not be obvious to take a leap from a valproate-based treatment of AD of Ohuchida to a treatment for MCI.

Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

## CONCLUSION

Applicants request favorable consideration of the application and early allowance of the pending claims 44 and 53. The Examiner is invited to telephone the undersigned to discuss any issue pertaining to this response.

Respectfully submitted,



James F. Haley, Jr. (Reg. No. 27,794)
Attorney for Applicants

ROPES & GRAY LLP
Customer No. 1473
1211 Avenue of the Americas
New York, New York 10036
Tel.: (212) 596-9000
Fax: (212) 596-9090